MAYO CLINIC

Cardiorespiratory Fitness and Gray Matter Volume in the Temporal, Frontal, and Cerebellar Regions in the General Population

Katharina Wittfeld, PhD; Carmen Jochem, MD; Marcus Dörr, MD; Ulf Schminke, MD; Sven Gläser, MD; Martin Bahls, PhD; Marcello R.P. Markus, MD; Stephan B. Felix, MD; Michael F. Leitzmann, MD, PhD; Ralf Ewert, MD; Robin Bülow, MD; Henry Völzke, MD; Deborah Janowitz, MD; Sebastian E. Baumeister, PhD; and Hans Jörgen Grabe, MD

Abstract

Objective: To analyze the association between cardiorespiratory fitness (CRF) and global and local brain volumes.

Participants and Methods: We studied 2103 adults (21-84 years old) from 2 independent population-based cohorts (Study of Health in Pomerania, examinations from June 25, 2008, through September 30, 2012). Cardiorespiratory fitness was measured using peak oxygen uptake (VO_2peak), oxygen uptake at the anaerobic threshold (VO_2@AT), and maximal power output from cardiopulmonary exercise testing on a bicycle ergometer. Magnetic resonance imaging brain data were analyzed by voxel-based morphometry using regression models with adjustment for age, sex, education, smoking, body weight, systolic blood pressure, glycated hemoglobin level, and intracranial volume.

Results: Volumetric analyses revealed associations of CRF with gray matter (GM) volume and total brain volume. After multivariable adjustment, a 1−standard deviation increase in VO_2peak was related to a 5.31 cm^3 (95% CI, 3.27 to 7.35 cm^3) higher GM volume. Whole-brain voxel-based morphometry analyses revealed significant positive relations between CRF and local GM volumes. The VO_2peak was strongly associated with GM volume of the left middle temporal gyrus (228 voxels), the right hippocampal gyrus (146 voxels), the left orbitofrontal cortex (348 voxels), and the bilateral cingulate cortex (68 and 43 voxels).

Conclusion: Cardiorespiratory fitness was positively associated with GM volume, total brain volume, and specific GM and white matter clusters in brain areas not primarily involved in movement processing. These results, from a representative population sample, suggest that CRF might contribute to improved brain health and might, therefore, decelerate pathology-specific GM decrease.

 ■ Mayo Clin Proc. 2020;95(1):44-56

For editorial comment, see page 6

From the German Center for Neurodegenerative Disease, Site Rostock/Greifswald, Germany (K.W., H.J.G.); Depart-

Affiliations continued at the end of this article.

According to the World Health Organization, dementia is a global epidemic, with 50 million people affected and estimated economic costs of approximately US $818 billion per year globally.[1] Therefore, dementia risk reduction is a focus of current research in addition to treatment and cure.[2] Physical inactivity is discussed as 1 of 7 risk factors for Alzheimer disease.[3] Cardiorespiratory fitness (CRF), which refers to the ability of the circulatory and respiratory systems to supply oxygen during physical activity, represents a major component of physical fitness and can be enhanced through regular physical activity.[4] Furthermore, CRF is a more valid and objective measure of physical activity compared with self-reported physical activity.[5]

Higher CRF is associated with lower risks of cardiovascular diseases[4,6] and metabolic syndrome,[7,8] which overlap with risk factors for Alzheimer disease[3] and vascular

dementia:[9] diabetes mellitus, hypertension, obesity, depression, smoking, and low educational level. Moreover, CRF is inversely associated with depression severity[10] and cancer mortality.[11]

Current literature suggests a positive relationship between CRF and gray matter (GM) volumes of the prefrontal cortex and the hippocampus.[12] Findings concerning white matter (WM) volumes are heterogeneous but point to higher WM volumes, fewer WM lesions, and improved WM microstructure in relation to higher physical fitness.[13] Existing studies were often limited by small study samples (rarely exceeding a few hundred participants), strongly selected patient groups (such as those with multiple sclerosis, heart failure, Alzheimer disease, or mild cognitive impairment), or restriction to older adults. Thus, larger, well-powered studies are needed to provide conclusive evidence for effects of CRF on specific brain regions.

Given the beneficial effects of physical activity and exercise on cognitive decline and dementia, as suggested by meta-analyses of observational studies,[14,15] we expect that high CRF may counteract brain atrophy related to brain aging and dementia. We used data from 2103 adults aged 21 to 84 years from 2 independent population-based cohorts (Study of Health in Pomerania [SHIP] and SHIP-Trend)[16] to investigate the association between CRF measurements as assessed by standardized cardiopulmonary exercise testing (CPET) and brain volumes. We conducted state-of-the-art voxel-based morphometry (VBM) analyses to evaluate potential GM and WM associations on a more precise level of spatial resolution.

PARTICIPANTS AND METHODS

General Population Samples

SHIP consists of 2 independent population-based samples of adults from a northeastern German region. In brief, the first sample (SHIP-0) was examined from 1997 through 2001. SHIP-0 was a stratified cluster-random sample of 7008 individuals; of the net sample (without migrated or deceased persons) of 6265 eligible individuals, 4308 (2192 women) participated (response rate, 68.8%). A second examination cycle (SHIP-1) was conducted from 2002 through 2006 and comprised 3300 participants. From June 25, 2008, through September 30, 2012, a third examination cycle was conducted (SHIP-2, N=2333). Concurrent with SHIP-2, a new age- and sex-stratified random sample, SHIP-Trend-0, of 10,000 individuals (net sample size of 8826) was drawn and 4420 (2275 women) participated (response rate, 50.1%).[16] Examinations for SHIP-Trend-0 were conducted from September 1, 2008, through September 30, 2012. More details about the study designs, recruitment, and procedures have been published elsewhere.[16]

Individuals from SHIP-2 and SHIP-Trend-0 were invited to participate in CPET and whole-body magnetic resonance imaging (MRI). The CPET was completed by 3214 participants (SHIP-2: n=1360 and SHIP-Trend-0: n=1854). Whole-body MRIs were acquired from 3317 participants (SHIP-2, n=1163 and SHIP-Trend-0: n=2154) who were free of any of the exclusion criteria for MRI (eg, cardiac pacemakers, pregnancy).[17] Complete data sets (including MRI, CPET, and covariates for adjustments) were available for 2494 individuals. We excluded individuals with chronic pulmonary diseases (including chronic bronchitis, emphysema, phthisis, and bronchial asthma), which left 2378 participants. The MRI quality control encompasses the exclusion of medical conditions (eg, a history of cerebral tumor, stroke, Parkinson disease, multiple sclerosis, epilepsy, hydrocephalus, enlarged ventricles, pathologic lesions) and technical reasons (eg, severe movement artifacts or strong inhomogeneity of the magnetic field), which yielded 2139 individuals. Based on a homogeneity check, which is implemented as a data quality check in the Computational Anatomy Toolbox 12 (CAT12), we excluded another 36 individuals defined as extreme outliers. The final sample consisted of 2103 participants (1104 women).

All the participants gave written informed consent, and the ethics committee of the University of Greifswald approved the study protocol.

Imaging and VBM

All images were obtained using a 1.5-T Siemens MRI scanner (MAGNETOM Avanto; Siemens Healthcare). The brain volumes total GM, total WM, and total brain volume (TBV) were derived from isotropic T1-weighted head MRIs with the fully automated recon-all pipeline of FreeSurfer 5.1.[18]

For the VBM analyses we used SPM12 (Wellcome Trust Centre for Neuroimaging, University College London) and CAT12 (developed by Christian Gaser, University of Jena, http://www.neuro.uni-jena.de) to preprocess the data and conduct the analyses. A detailed description of the MRI parameters and preprocessing of the data can be found in the Supplemental Appendix (available online at http://www.mayoclinicproceedings.org).

Assessment of CRF

Symptom-limited CPET using a calibrated electromagnetically braked cycle ergometer (Ergoselect 100; Ergoline) was performed according to a modified Jones protocol: 3 minutes of rest, 1 minute of unloaded cycling at 60 revolutions per minute, stepwise increase in workload of 16 W/min until symptom limited or terminated due to chest pain or electrocardiographic abnormalities, and 5 minutes of recovery.[19] Gas exchange and ventilatory variables were analyzed breath by breath averaged over 10-second intervals using a VIASYS Healthcare system (Oxycon Pro, Combitox mask). Peak oxygen uptake (VO_2peak), oxygen uptake at the anaerobic threshold (VO_2@AT), and maximal power output (W_{max}) were determined as previously described.[20]

Statistical Analyses

Detailed characteristics of the study participants stratified by sex are given in Table 1. Associations of VO_2peak, VO_2@AT, and W_{max} (modeled as continuous covariates) and brain volumes were examined using multivariable truncated regression models[21] in Stata 14.1 (StataCorp LLC). Multivariable fractional polynomials[22] were used to test for nonlinear associations. Because linearity was established in all the models, we report

TABLE 1. Characteristics of the Study Sample by Sex[a]

Characteristic	Total sample (N=2103)	Men (n=999)	Women (n=1104)
Age (y), mean ± SD	52.3±13.1	52.1±13.4	52.5±12.8
Intracranial volume (cm^3), mean ± SD	1576.2±162.3	1683.1±133.2	1479.5±120.0
Total brain volume (cm^3), mean ± SD	1151.7±118.6	1225.1±103.7	1085.3±88.3
Cardiorespiratory fitness, mean ± SD			
VO_2peak (mL/min)	1999.6±656.6	2460.6±7.4	1582.4±366.1
VO_2@AT (mL/min)	1010.1±283.6	1166.1±281.7	868.9±198.7
W_{max} (W)	162.0±52.2	198.3±46.3	129.1±31.4
Relative cardiorespiratory fitness, mean ± SD[b]			
VO_2peak (mL/min/kg)	25.3±7.2	28.5±7.4	22.3±5.5
VO_2@AT (mL/min/kg)	12.9±3.3	13.5±3.5	12.3±3.0
W_{max} (W/kg)	2.1±0.6	2.3±0.6	1.8±0.5
School education (% <10 y)	16.3	16.1	16.4
Current smoker (%)	21.6	23.6	19.8
Body weight (kg), mean ± SD	79.4±15.0	87.4±12.8	72.2±13.1
Systolic blood pressure (mm Hg), mean ± SD	127.6±17.2	133.8±15.4	122.1±16.8
Glycated hemoglobin (%), mean ± SD	5.3±0.7	5.4±0.8	5.2±0.7

[a]VO_2peak = peak oxygen uptake; VO_2@AT = oxygen uptake at the anaerobic threshold; W_{max} = maximal power output.
[b]Normalized by body weight.

Mayo Clin Proc. ■ January 2020;95(1):44-56 ■ https://doi.org/10.1016/j.mayocp.2019.05.030
www.mayoclinicproceedings.org

regression coefficients per 1−standard deviation (SD) increase in VO_2peak, VO_2@AT, and W_{max}. All the models were adjusted for age (modeled continuously using restricted cubic splines), sex (male, female), educational level (<10, 10, >10 years in school), smoking status (never, former, current), body weight (continuous), systolic blood pressure (continuous), glycated hemoglobin level (continuous), intracranial volume (continuous) (except for the model for TBV[23]), and cohort (SHIP-2, SHIP-Trend-0).

For the VBM analyses, we used SPM12 to analyze the preprocessed GM and WM segments. For each exposure variable (VO_2peak, VO_2@AT, and W_{max}), we conducted a linear regression model with the same set of covariates, including intracranial volume. In addition, VBM analyses were adjusted for the index of quality rating generated during preprocessing in CAT12. We used the Masking Toolbox[24] to define explicit masks to limit the number of voxels entering the VBM analyses on GM and WM.

The statistical threshold for significant voxels was set to a familywise error−corrected peak-level P ($P_{peak,FWE}$)<.05. The labeling of the significant clusters was performed using the xjView toolbox (http://www.alivelearn.net/xjview) on the basis of the automated anatomical labeling atlas.[25] Unless otherwise mentioned, only clusters with a cluster size of at least 30 voxels are provided, which exceeds the estimated expected number of voxels given in the SPM12 report for this data set.

To evaluate the decline of CRF with aging and the age-related decline of the brain volumes, we tested the interaction of CRF measures and age in VBM analyses with the same set of covariates as for the main effects VBM analyses but using age as a linear term in the interaction model. For these VBM analyses, we set the statistical threshold for significant voxels after correction for multiple testing to $P_{peak,FWE}$<.025 because we performed a 2-sided test for effects of the interaction term. The adjusted brain volumes, used for illustrative purposes of the interaction, were obtained by calculating the residuals of the brain volumes in a linear regression adjusting for the same set of covariates excluding age and the CRF measure.

Often, CRF measures are being analyzed as ratios (ie, VO_2peak to body weight) with the aim of removing confounding effects of body weight on CRF. To be able to compare the results with the existing literature, we evaluated the association of relative fitness measures (VO_2peak to body weight, VO_2@AT to body weight, and W_{max} to body weight ratios) with segmented brain volumes (total GM, total WM, and TBV) and in the VBM analyses. We used the same set of confounders except for body weight.

RESULTS

The analyses included 2103 individuals (1104 women) aged 21 to 84 years (mean ± SD age, 52.34±13.10 years). See Supplemental Figure 1 (available online at http://www.mayoclinicproceedings.org) for a visual impression of the age distribution. Further sample characteristics stratified by sex are provided in Table 1.

Associations Between CRF and Brain Volumes

Volumetric analyses revealed consistent positive associations of measures of CRF with TBV and GM volume but not with total WM volume (Table 2). The 1-SD changes in VO_2peak, VO_2@AT, and W_{max} were associated with 5.31 cm^3 (95% CI, 3.27 to 7.35 cm^3), 1.79 cm^3 (95% CI, 0.22 to 3.36 cm^3), and 5.70 cm^3 (95% CI, 3.61 to 7.80 cm^3) increases in GM volume, respectively. The TBV was higher by 19.93 cm^3 (95% CI, 13.82 to 26.03 cm^3), 7.70 cm^3 (95% CI, 2.98 to 12.43 cm^3), and 21.38 cm^3 (95% CI, 15.09 to 27.66 cm^3) per 1-SD change in VO_2peak, VO_2@AT, and W_{max}, respectively. Figure 1 illustrates the associations of the CRF measure VO_2peak with the multivariable-adjusted brain GM volume, WM volume, and TBV.

Whole-Brain VBM Analyses on CRF Measures for GM and WM

The VBM analyses for exposures VO_2peak and W_{max} revealed several significant ($P_{peak,FWE}\leq.05$) clusters that were positively associated with GM (Table 3 and Figure 2).

TABLE 2. Association Between Cardiorespiratory Fitness and Segmented Brain Volumes in the 2103 Study Participants[a,b]

Cardiorespiratory fitness	Volume (cm^3), $ß^t$ (95% CI) [*P* value]		
	Gray matter	White matter	Total brain
VO_2peak (mL/min, per 1 SD)	5.31 (3.27 to 7.35) [<.001]	0.27 (−1.99 to 2.54) [.81]	19.93 (13.82 to 26.03) [<.001]
VO_2@AT (mL/min, per 1 SD)	1.79 (0.22 to 3.36) [.03]	−0.36 (−2.09 to 1.37) [.68]	7.70 (2.98 to 12.43) [.001]
W_{max} (W, per 1 SD)	5.70 (3.61 to 7.80) [<.001]	0.09 (−2.24 to 2.42) [.94]	21.38 (15.09 to 27.66) [<.001]

[a] $ß^t$ = truncated regression coefficient per study-specific standard deviation, truncated at minimum and maximum of dependent variable; SD = standard deviation; VO_2peak = peak oxygen uptake; VO_2@AT = oxygen uptake at the anaerobic threshold; W_{max} = maximal power output.

[b] Values are adjusted for age (modeled continuously using restricted cubic splines), sex (male, female), educational level (<10, 10, >10 years in school), smoking status (never, former, current), body weight (continuous), systolic blood pressure (continuous), glycated hemoglobin level (continuous), intracranial volume (continuous; not in the model for total brain volume), and cohort (Study of Health in Pomerania [SHIP]-2, SHIP-Trend-0). One regression model was run for each exposure-outcome combination.

The high correlation between VO_2peak and W_{max} (Pearson correlation coefficient r=0.92) explains the large overlap of the significant clusters for both exposures. Mainly regions in the hippocampus/parahippocampus, the temporal gyrus, the fusiform gyrus, the cingulate cortex, the orbitofrontal cortex, the cerebellum, the left caudate nucleus, and the left thalamus were associated with the CRF functions VO_2peak and W_{max}.

The VBM analyses on VO_2@AT revealed only 1 significant cluster that correlated positively with GM and exceeded a cluster size of at least 30 voxels: left middle temporal gyrus (65 voxels, $P_{peak,FWE}$=.003, [−65, −29, −3]) (Table 3).

The whole-brain VBMs on WM yielded only a few statistically significant clusters that correlated positively with W_{max} (268 voxels in the left putamen, pallidum, and insula; 64 sublobar voxels close to the right pallidum; and 10 voxels in the left olfactory cortex and putamen). Detailed results are summarized in Supplemental Table 1 (available online at http://www.mayoclinicproceedings.org).

The WM VBM analyses on VO_2peak and VO_2@AT did not reveal any statistically significant results.

Analyses of CRF and Age-Related Decline of the Brain Volume

Studying the interaction of CRF and age on the GM using VBM analyses, we found that the association effects of VO_2peak and W_{max} on clusters in the left (VO_2peak: 352 voxels; W_{max}: 472 voxels) and right (VO_2peak: 156 voxels; W_{max}: 184 voxels) hippocampal region were significantly increased by age. The hippocampal clusters associated with the interaction of W_{max} with age overlapped with significant results of the main effect analysis for W_{max} (left: 10 voxels, right: 38 voxels).

To illustrate these findings we extracted the GM volume of 2 spheres with a radius of 5 mm surrounding the significant peak voxels in the left [−26, −21, −11] and right [27, −18, −12] hippocampus for all 2103 participants and plotted the association of CRF measurements and the adjusted brain volumes (see the Participants and Methods section) by age tertiles (Supplemental Figure 2, available online at http://www.mayoclinicproceedings.org).

We further revealed significant interactions for CRF and age for a cluster in the left thalamus (VO_2peak: 48 voxels) and in the right middle frontal and superior frontal gyrus (VO_2peak: 354 voxels, W_{max}: 302 voxels). Detailed results are summarized in Supplemental Table 2 (available online at http://www.mayoclinicproceedings.org). The VBM analysis of the interaction of VO_2@AT with age did not reveal any statistically significant results.

Associations of Relative CRF Measures With Global and Local GM Volumes

Volumetric analyses revealed positive associations of total GM volume with the relative CRF measures VO_2peak to body weight and W_{max} to body weight ratios

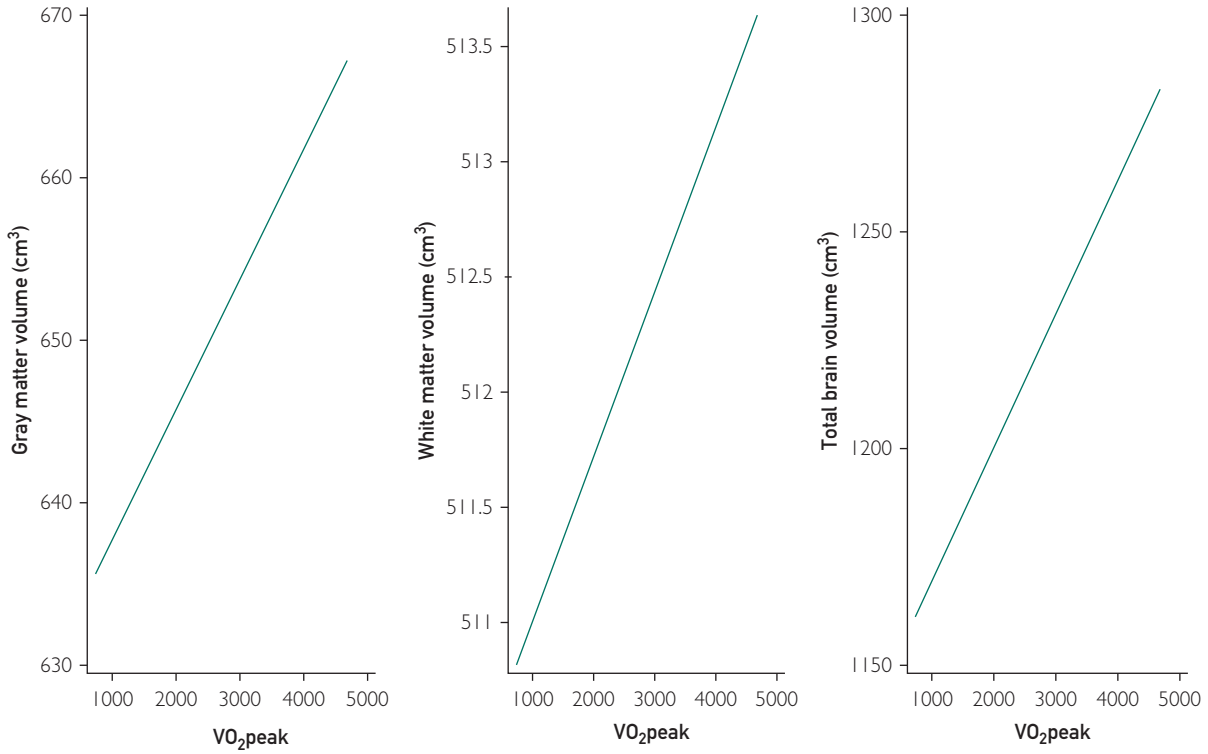

FIGURE 1. Association between peak oxygen uptake (VO_2peak) and brain volumes. The brain volumes were multivariable adjusted for age (modeled continuously using restricted cubic splines), sex (male, female), educational level (<10, 10, >10 years in school), smoking status (never, former, current), body weight (continuous), systolic blood pressure (continuous), glycated hemoglobin level (continuous), intracranial volume (continuous; not in the model for total brain volume), and cohort (Study of Health in Pomerania [SHIP]-2, SHIP-Trend-0).

and of TBV with VO_2peak to body weight ratio. The 1-SD changes in VO_2peak to body weight and W_{max} to body weight ratios were associated with 3.08 cm^3 (95% CI, 1.44 to 4.72 cm^3) and 2.87 cm^3 (95% CI, 1.20 to 4.54 cm^3) increases in GM volume, respectively. Also, TBV was higher by 6.88 cm^3 (95% CI, 1.88 to 11.88 cm^3) per 1-SD change in VO_2peak to body weight. We detected no significant associations of the relative CRF measures (VO_2peak to body weight, VO_2@AT to body weight, and W_{max} to body weight ratios) with total WM volume (Supplemental Table 3, available online at http://www.mayoclinicproceedings.org).

The VBM analyses for exposures VO_2peak to body weight and W_{max} to body weight ratios revealed several significant ($P_{peak,FWE} \leq .05$) clusters that were positively associated with GM volume (Supplemental Table 4, available online at http://www.mayoclinicproceedings.org). Comparing these results with the results from the VBM analysis of VO_2peak and W_{max} we found an overlap of 78 voxels in the left middle temporal gyrus that are significantly associated with VO_2peak and VO_2peak to body weight ratio. For the CRF measures W_{max} and W_{max} to body weight ratio, the overlap of the significant results sums up to 395 voxels distributed in 5 clusters located in the left middle temporal gyrus (215 voxels), the left gyrus rectus (22 voxels), the left orbital part of the superior and inferior frontal gyrus (64 voxels), the left angular gyrus (47 voxels), and the left insula (47 voxels). The VO_2@AT to body weight ratio revealed no significant associations in the volumetric analyses and the VBM analysis.

TABLE 3. VBM Results for Cardiorespiratory Fitness[a,b]

Cluster size (in voxels)	AAL regions	Brodmann areas	$P_{peak,FWE}$	*t* score	Cohen's D	Stereotaxic coordinates (mm) x	y	z
VO_2peak								
228	L middle temporal gyrus	22, 21	<.001	5.45	0.24	−65	−45	5
			.003	5.22	0.23	−66	−32	−2
348	L gyrus rectus, L medial orbital frontal gyrus	11, 25, 32	<.001	5.43	0.24	−5	36	−17
			.009	4.96	0.22	−11	47	−15
146	R parahippocampal gyrus	35, 28, 36	.004	5.15	0.23	18	−14	−30
83	L thalamus	—	.006	5.06	0.22	−8	−21	18
46	L medial superior frontal cortex, L anterior cingulate cortex, R anterior cingulate cortex	9	.009	4.98	0.22	0	42	24
68	L middle cingulate cortex, R middle cingulate cortex, R supplementary motor area	31, 24	.01	4.87	0.21	0	−5	47
			.02	4.82	0.21	−2	−17	45
43	R middle cingulate cortex, L medial superior frontal cortex, L supplementary motor area, R medial superior frontal cortex	32	.02	4.79	0.21	5	24	38
VO_2@AT								
65	L middle temporal gyrus	21	.003	5.20	0.23	−65	−29	−3
W_{max}								
624	L middle temporal gyrus, L superior temporal gyrus	21, 22	<.001	6.51	0.29	−68	−33	0
			<.001	5.99	0.26	−68	−42	5
			.005	5.10	0.22	−65	−20	−6
1812	L gyrus rectus, R gyrus rectus, L medial orbital frontal gyrus, L superior frontal gyrus (orbital part), L caudate nucleus, L olfactory cortex, L inferior frontal gyrus (orbital part), R superior frontal gyrus (orbital part), R medial orbital frontal gyrus	11, 25, 47, 10, 32	<.001	5.90	0.26	−6	35	−17
			<.001	5.79	0.25	−11	23	−12
			<.001	5.66	0.25	8	29	−17
290	L angular gyrus	39, 40, 7	<.001	5.78	0.25	−53	−66	39
748	L inferior temporal gyrus, L fusiform gyrus, L parahippocampal gyrus, L temporal pole (middle gyrus), L middle temporal gyrus	20, 21, 36, 28, 38, 35	<.001	5.65	0.25	−35	−2	−38
			<.001	5.55	0.24	−44	5	−36
			.005	5.09	0.22	−42	−2	−44
1289	R parahippocampal gyrus, R hippocampus, R fusiform gyrus, R temporal pole (middle gyrus), R inferior temporal gyrus, R amygdala, R temporal pole (superior gyrus), R cerebellum 4_5	36, 35, 28, 38, 20	<.001	5.64	0.25	36	−23	−18
			<.001	5.64	0.25	24	−12	−12
			<.001	5.62	0.25	33	0	−38
264	L Cerebellum 4_5, L fusiform gyrus, L cerebellum 6, L lingual gyrus	37, 19	.001	5.39	0.24	−21	−51	−15
134	L thalamus	—	.002	5.30	0.23	−8	−21	18
337	L hippocampus, L parahippocampal gyrus	28, 35	.003	5.21	0.23	−24	−15	−12
			.005	5.08	0.22	−21	−18	−23
80	R middle temporal gyrus, R inferior temporal gyrus	21, 20	.004	5.15	0.23	60	−17	−15
			.006	5.05	0.22	53	−12	−21

Continued on next page

TABLE 3. Continued

Cluster size (in voxels)	AAL regions	Brodmann areas	$P_{peak,FWE}$	*t* score	Cohen's D	Stereotaxic coordinates (mm)		
						x	y	z
W_{max}, continued								
84	L temporal pole (superior gyrus), L amygdala	34, 38, 28	.01	4.94	0.22	−29	3	−20
47	L insula, L inferior frontal gyrus (orbital part), L inferior frontal gyrus (triangular part)	–	.01	4.90	0.21	−36	21	−5

[a]AAL = automated anatomical labeling; CAT12 = Computational Anatomy Toolbox 12; L = left hemisphere; $P_{peak,FWE}$ = familywise error–corrected peak-level *P*; R = right hemisphere; VBM= voxel-based morphometry; VO_2peak = peak oxygen uptake; VO_2@AT = oxygen uptake at the anaerobic threshold; W_{max} = maximal power output.

[b]The VBM analyses were adjusted for age (modeled continuously using restricted cubic splines), sex (male, female), educational level (<10, 10, >10 years in school), smoking status (never, former, current), body weight (continuous), systolic blood pressure (continuous), glycated hemoglobin level (continuous), intracranial volume (continuous), cohort (Study of Health in Pomerania [SHIP]-2, SHIP-Trend-0), and CAT12 quality measure index of quality. The VBM analyses revealed significant ($P_{peak,FWE}$<.05) positive associations of gray matter with VO_2peak, VO_2@AT, and W_{max} (2103). The AAL regions and Brodmann areas are listed according to the numbers of voxels they contribute to the respective cluster. Only clusters with a cluster size of at least 30 voxels are provided, which exceeds the estimated expected number of voxels given in the SPM12 report.

DISCUSSION

Countries worldwide are facing aging societies. And it is essential to identify strategies to slow brain aging and help preserve brain structure and functionality in older individuals. Cardiorespiratory fitness is considered a key factor reducing the risk of death, cardiovascular morbidity, several cancers, and possibly brain atrophy.

Well-powered randomly selected population samples with deeply phenotyped measures of the brain are necessary to provide robust evidence for an effect of CRF on GM and WM volume on a high spatial resolution analyses. Based on population-based data from the 2 SHIP cohorts, we contributed to closing this gap by analyzing structural MRI data and parameters of CRF as measured by CPET in a large sample.

The present findings of positive relationships between the 3 CRF measures (VO_2peak, VO_2@AT, and W_{max}) and segmented brain volumes (total GM volume and TBV) are in line with the previous literature.[12,26]

Zooming into a fine spatial resolution, VBM analyses on GM segmentations revealed several large clusters of voxels with $P_{peak,FWE}<.05$ that were positively associated with CRF. Thus, VO_2peak and W_{max} were significantly associated with greater GM volumes in the hippocampus/parahippocampus, the temporal gyrus, the fusiform gyrus, the cingulate cortex, the orbitofrontal cortex, the cerebellum, the left caudate nucleus, and the left thalamus.

The present findings in the hippocampus and the orbitofrontal cortex, which is a part of the prefrontal cortex, are in line with the most robustly replicated results throughout the physical activity and CRF literature related to brain volumes.[12,26,27] The hippocampus itself plays a central role in memory-related functions (coding of memories, long-term memory, and retrieval)[28] and in stress regulation.[29] Hippocampus atrophy was found to be associated with several diseases and disorders, such as Alzheimer disease,[30] depression,[31] and schizophrenia.[32] The orbitofrontal cortex is involved in decision making for emotional and reward-related behaviors.[33] Potential

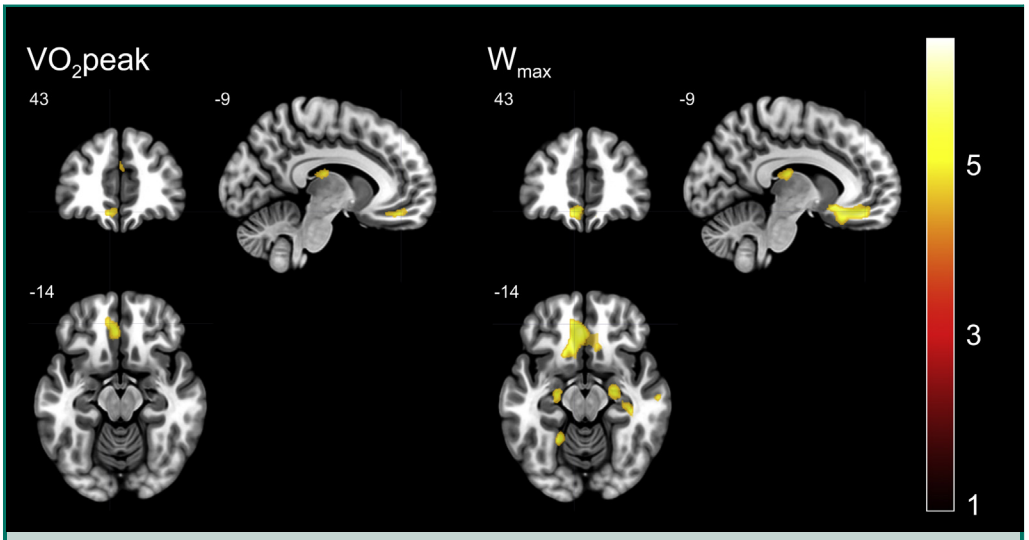

FIGURE 2. Results of the voxel-based morphometry (VBM) analyses of peak oxygen uptake (VO_2peak) and maximal power output (W_{max}). The VBM analyses revealed significant (familywise error–corrected peak-level $P<.05$) positive associations of VO_2peak and W_{max} with gray matter (N=2103). The 2 VBM analyses were adjusted for age (modeled continuously using restricted cubic splines), sex (male, female), educational level (<10, 10, >10 years in school), smoking status (never, former, current), body weight (continuous), systolic blood pressure (continuous), glycated hemoglobin level (continuous), intracranial volume (continuous), cohort (Study of Health in Pomerania [SHIP]-2, SHIP-Trend-0), and Computational Anatomy Toolbox 12 quality measure index of quality rating. Significant clusters with a cluster size of at least 30 voxels are pictured.

endocrinal mechanisms of anti-inflammatory factors and neurotrophins such as brain-derived neurotrophic factor that have been found to be linked to increased physical activity and CRF[34,35] might play a major role in neuroplastic effects, neuromodulation, and recovery, which might lead to improved brain health and slower cognitive decline.[36]

In addition, the observed interaction of age with VO_2peak and W_{max} on the hippocampal volume indicates a stronger benefit of higher CRF in those 45 years and older.

Significant parts of 3 larger clusters (right hemisphere: 182 voxels out of 1289 voxels; left hemisphere: 210 voxels out of 748 voxels; and 68 voxels out of 264 voxels) associated with W_{max} lie in the right and left fusiform gyri, respectively. The fusiform gyrus is involved in face recognition,[37] is seriously atrophied in various forms of dementia,[38] and was found to be linked with alexithymia.[39]

The lack of well-powered studies that conducted VBM analyses using measures of CRF as exposure variables rather than type and intensity of physical activity based on self-reports or short time measurement via actimeters makes it difficult to find corresponding valid results. In addition, CRF is not only affected by continuous aerobic physical activity but also by behavioral risk factors, genetics, and comorbid conditions.[40,41] Batouli and Saba[42] gave a good overview of the current literature about physical activity and CRF markers, but their conclusion that "at least eighty percent of the brain gray matter is modifiable by physical activity" cannot be supported by the findings from our well-powered and representative analyses.

A previous study by Verstynen et al[43] of 179 individuals found a positive association of CRF (as assessed by VO_2peak) with the volume of the caudate nucleus that we can support with the finding in the left caudate nucleus. Furthermore, Whiteman et al,[44] who conducted a VBM analysis of VO_2peak on 33 individuals, revealed several clusters in the inferior and middle temporal gyrus of the right hemisphere that we support

Mayo Clin Proc. ■ January 2020;95(1):44-56 ■ https://doi.org/10.1016/j.mayocp.2019.05.030
www.mayoclinicproceedings.org

and extend with the present bilateral findings for these brain regions.

Brockett et al[45] observed an increase in the body area of astrocytes in the hippocampus, medial prefrontal cortex, and orbitofrontal cortex when they compared running with sedentary behavior in an animal exercise model. This is of particular interest because we observed several significant clusters in the orbitofrontal cortex that were positively associated with VO_2peak and W_{max}.

The results of the VBM analyses on VO_2peak and W_{max} showed great spatial overlap, which could be explained by the high correlation between VO_2peak and W_{max} (r=0.92). Particularly notable is the fact that the clusters for W_{max} were much larger than those for VO_2peak. Maximal power output is a marker for exhausting activities that require intense muscle work and power, whereas VO_2peak characterizes the maximum oxygen uptake capacity of the lung.[46] Therefore, a potential explanation for this observation is the increased activation of muscle cell–related pathways that release neurotrophic myokines or metabolites into the blood circulation and promote the production of various factors from nonmuscle tissues such as the liver, which might further contribute to the expression of neurotrophins such as brain-derived neurotrophic factor in the brain.[47]

An alternative explanation is that motivational and emotional individual differences, which could be directly associated with the increased GM volumes found in the present study, are responsible for higher physical activities and, therefore, higher CRF. Thus, higher CRF would be the result of differences in brain structure and function and not vice versa. Longitudinal analyses would be needed to differentiate between these 2 rivaling hypotheses.

In contrast to VO_2peak and W_{max}, VO_2@AT showed much weaker associations with segmented brain volumes of total GM volume and TBV and with local brain regions in the VBM analyses. Thus, the anaerobic/aerobic threshold is probably not relevant to the CRF-related muscle-brain communication.

Most of the clusters revealed by the VBM analyses on CRF parameters are not primarily associated with the motor cortex or movement processing. Only 2 small clusters of 68 and 43 voxels, associated with VO_2peak, comprise small parts of the supplementary motor area in the right and left hemisphere, respectively, and 1 cluster was located in the cerebellum (264 voxels associated with W_{max}), which might also play a role in movement processing.[48] Physical exercises that go along with higher CRF could be so broadly distributed over a wide range of activities in the present study participants that potential neuroplastic changes in the motor brain system were not locally specific enough to yield volumetric signals. Furthermore, the review by Voelcker-Rehage and Niemann[49] provides a detailed overview of the structural and functional effects of different types of physical activity, which are not located only in motor areas of the brain.

Although we did not detect a significant association between CRF and total WM volume in volumetric analysis, the VBM analyses revealed 3 clusters with a positive relationship between the CRF marker W_{max} and WM volume. Because VBM analyses on structural MRI data are not the favored approach to study WM alterations, we recommend using diffusion tensor imaging analyses in future research.

We studied 2 methodical approaches to take the dependence of the CRF measures from the body composition into account: the adjustment for body weight as a covariable in regression models and relative CRF measure normalized body weight (ie, VO_2peak to body weight ratio). The results for VO_2peak and W_{max} for the global brain volumes (total GM volume and TBV) are similar but with smaller effects when the ratio method was applied. Both methods revealed several significant clusters in the VBM analyses. The clusters are spread differently over the brain for both methods but share a certain amount of overlap. A potential explanation might be the violation of one of the critical assumptions made by the ratio method (linearity and zero intercept), which might introduce a bias.[50,51]

The present study has several limitations that need to be considered when interpreting the findings. First, CPET and MRI were assessed in a cross-sectional design. Consequently, reverse causation (ie, individuals with greater brain volumes have higher CRF) cannot be excluded. Second, although we adjusted for a variety of confounding factors, residual confounding due to other unmeasured factors cannot be ruled out. Third, due to the exclusion criteria for ergometer testing and MRI, a potential bias, compared with the randomly selected general population sample, might have been introduced. Thus, longitudinal studies are required in the future.

CONCLUSION

The results of this study support the hypothesis that higher CRF is associated with larger brain volumes in several brain regions that are not primarily connected to motor-related functions. Older people seem to have a stronger benefit in the memory-sensitive hippocampal region by higher CRF.

ACKNOWLEDGMENTS

SHIP is part of the Community Medicine Research net (http://www.medizin.uni-greifswald.de/icm) of University Medicine Greifswald, which is supported by the German Federal State of Mecklenburg–West Pomerania. The MRIs in SHIP and SHIP-Trend were supported by a joint grant from Siemens Healthineers, Erlangen, Germany, and the Federal State of Mecklenburg–West Pomerania. This study was further supported by the German Center for Cardiovascular Research, the German Center for Neurodegenerative Diseases, and the EU Joint Programme – Neurodegenerative Disease Research funding for BRIDGET (FKZ:01ED1615).

The data set of the SHIP cohorts used and analyzed during the present study cannot be made publically available owing to the informed consent of the study participants, but it can be accessed through a data application form available at https://fvcm.med.uni-greifswald.de/ for researchers who meet the criteria for access to confidential data.

Drs Wittfeld, Jochem, Baumeister, and Grabe contributed equally to this work.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **AAL** = automated anatomical labeling; **CAT12** = Computational Anatomy Toolbox 12; **CPET** = cardiopulmonary exercise testing; **CRF** = cardiorespiratory fitness; **FWE** = familywise error; **GM** = gray matter; **MRI** = magnetic resonance imaging; $P_{peak.FWE}$ = familywise error–corrected peak-level *P*; **SD** = standard deviation; **SHIP** = Study of Health in Pomerania; **TBV** = total brain volume; **VBM** = voxel-based morphometry; VO_2**@AT** = oxygen uptake at the anaerobic threshold; VO_2**peak** = peak oxygen uptake; **WM** = white matter; W_{max} = maximal power output

Affiliations (Continued from the first page of this article.): ment of Psychiatry and Psychotherapy (K.W., D.J., H.J.G.), Department of Internal Medicine B (M.D., S.G., M.B., M.R.P.M., S.B.F., R.E.), Department of Neurology (U.S.), Institute of Diagnostic Radiology and Neuroradiology (R.B.), and Institute for Community Medicine (H.V., S.E.B.), University Medicine Greifswald, Germany; Department of Epidemiology and Preventive Medicine, University of Regensburg, Germany (C.J., M.F.L.); German Centre for Cardiovascular Research, Partner Site Greifswald, Germany (M.D., M.B., M.R.P.M., S.B.F., H.V.); German Center for Diabetes Research, Partner Site Greifswald, Germany (M.R.P.M., H.V.); Chair of Epidemiology, Ludwig-Maximilians-Universität München, UNIKA-T Augsburg, Germany (S.E.B.); and Independent Research Group Clinical Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Munich, Germany (S.E.B.).

Grant Support: This study was funded by grants BMBF 01ZZ96030 and BMBF 01ZZ0701 from the German Federal Ministry of Education and Research. This study was supported by the EUJPND Funding for BRIDGET (FKZ:01ED1615). SHIP is part of the Community Medicine Research net of the University of Greifswald, Germany, which is funded by the Federal Ministry of Education and Research (grants 01ZZ9603, 01ZZ0103, and 01ZZ0403), the Ministry of Cultural Affairs and the Social Ministry of the Federal State of Mecklenburg-West Pomerania. MRI scans in SHIP and SHIP-Trend have been supported by a joint grant from Siemens Healthcare, Erlangen, Germany, and the Federal State of Mecklenburg–West Pomerania.

Potential Competing interests: Dr Gläser has served as a board member for Roche Pharma, Boehringer Ingelheim, Novartis, and Berlin-Chemie and on the speaker's bureau for Actelion Pharma, Roche Pharma, Boehringer Ingelheim, Astra, and Novartis. Dr Ewert has received travel expenses from Actelion GmbH and OMT GmbH; has served as a board member for Actelion GmbH and Boehringer Ingelheim GmbH; has received grants from Actelion and Boehringer Ingelheim GmbH; and has received payment for lectures from Boehringer Ingelheim, Actelion Germany, Bayer Vital GmbH, OMT GmbH, AstraZenica, and CareFusion. Dr Janowitz has received grant support from DGF and has served on the speaker's bureau for Janssen-Cilag. Dr Baumeister has received research funding from the BMBF (German Ministry of Education and Research), EU, and Deutsche Krebshilfe. Dr Grabe has received travel grants and speaker's honoraria from Fresenius Medical Care and Janssen Cilag and research funding from the German Research Foundation, the German Ministry of Education and Research, the DAMP Foundation, Fresenius Medical Care, and the EU Joint Programme Neurodegenerative Disorders. The other authors report no competing interests.

Correspondence: Address to Katharina Wittfeld, PhD, German Center for Neurodegenerative Diseases, Rostock/Greifswald, Ellernholzstr. 1/2, 17475 Greifswald, Germany (Katharina.wittfeld@uni-greifswald.de).

REFERENCES

1. World Health Organization. Towards a Dementia Plan: A WHO Guide. . Published, http://www.who.int/mental_health/neurology/dementia/policy_guidance/en/ 2018. Accessed July 28, 2019.
2. Prince M, Wimo A, Guerchet M, Ali G-C, Wu Y-T, Prina M. *World Alzheimer Report 2015: The Global Impact of Dementia*. London, UK: Alzheimer's Disease International; 2015.
3. Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol*. 2011;10(9):819-828.
4. Myers J, McAuley P, Lavie CJ, Despres JP, Arena R, Kokkinos P. Physical activity and cardiorespiratory fitness as major markers of cardiovascular risk: their independent and interwoven importance to health status. *Prog Cardiovasc Dis*. 2015;57(4):306-314.
5. Swift DL, Lavie CJ, Johannsen NM, et al. Physical activity, cardiorespiratory fitness, and exercise training in primary and secondary coronary prevention. *Circ J*. 2013;77(2):281-292.
6. Gupta S, Rohatgi A, Ayers CR, et al. Cardiorespiratory fitness and classification of risk of cardiovascular disease mortality. *Circulation*. 2011;123(13):1377-1383.
7. Wedell-Neergaard AS, Krogh-Madsen R, Petersen GL, et al. Cardiorespiratory fitness and the metabolic syndrome: Roles of inflammation and abdominal obesity. *PLoS One*. 2018;13(3):1-16.
8. Ingle L, Mellis M, Brodie D, Sandercock GR. Associations between cardiorespiratory fitness and the metabolic syndrome in British men. *Heart*. 2017;103(7):516-520.
9. Kalaria RN, Maestre GE, Arizaga R, et al. Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors. *Lancet Neurol*. 2008;7(9):812-826.
10. Papasavvas T, Bonow RO, Alhashemi M, Micklewright D. Depression symptom severity and cardiorespiratory fitness in healthy and depressed adults: a systematic review and meta-analysis. *Sport Med*. 2016;46(2):219-230.
11. Schmid D, Leitzmann MF. Cardiorespiratory fitness as predictor of cancer mortality: a systematic review and meta-analysis. *Ann Oncol*. 2015;26(2):272-278.
12. Hall PA, Bickel WK, Erickson KI, Wagner DD. Neuroimaging, neuromodulation, and population health: the neuroscience of chronic disease prevention. *Ann N Y Acad Sci*. 2018;1428(1):240-256.
13. Sexton CE, Betts JF, Demnitz N, Dawes H, Ebmeier KP, Johansen-Berg H. A systematic review of MRI studies examining the relationship between physical fitness and activity and the white matter of the ageing brain. *Neuroimage*. 2016;131:81-90.
14. Blondell SJ, Hammersley-Mather R, Veerman J. Does physical activity prevent cognitive decline and dementia? a systematic review and meta-analysis of longitudinal studies. *BMC Public Health*. 2014;14:1-12.
15. Bherer L, Erickson KI, Liu-Ambrose T. A review of the effects of physical activity and exercise on cognitive and brain functions in older adults. *J Aging Res*. 2013;2013:657508.
16. Völzke H, Alte D, Schmidt CO, et al. Cohort profile: the study of health in Pomerania. *Int J Epidemiol*. 2011;40(2):294-307.
17. Hegenscheid K, Seipel R, Schmidt CO, et al. Potentially relevant incidental findings on research whole-body MRI in the general adult population: frequencies and management. *Eur Radiol*. 2013;23(3):816-826.
18. Fischl B, Salat DH, Busa E, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*. 2002;33(3):341-355.
19. Jones NL, Makrides L, Hitchcock C, Chypchar T, McCartney N. Normal standards for an incremental progressive cycle ergometer test. *Am Rev Respir Dis*. 1985;131(5):700-708.
20. Koch B, Schäper C, Ittermann T, et al. Reference values for cardiopulmonary exercise testing in healthy volunteers: the SHIP study. *Eur Respir J*. 2009;33(2):389-397.
21. Haahr ME, Fisher P, Holst K, et al. The 5-HT4 receptor levels in hippocampus correlates inversely with memory test performance in humans. *Hum Brain Mapp*. 2013;34(11):3066-3074.
22. Sauerbrei W, Royston P. Building multivariable prognostic and diagnostic models: transformation of the predictors by using fractional polynomials. *J R Stat Soc Ser A Stat Soc*. 1999;162(1):71-94.
23. O'Brien LM, Ziegler DA, Deutsch CK, Frazier JA, Herbert MR, Locascio JJ. Statistical adjustments for brain size in volumetric neuroimaging studies: some practical implications in methods. *Psychiatry Res*. 2011;193(2):113-122.
24. Ridgway GR, Omar R, Ourselin S, Hill DLG, Warren JD, Fox NC. Issues with threshold masking in voxel-based morphometry of atrophied brains. *Neuroimage*. 2009;44(1):99-111.
25. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage*. 2002;15(1):273-289.
26. Erickson KI, Leckie RL, Weinstein AM. Physical activity, fitness, and gray matter volume. *Neurobiol Aging*. 2014;35:S20-S28.
27. Killgore WDS, Olson EA, Weber M. Physical exercise habits correlate with gray matter volume of the hippocampus in healthy adult humans. *Sci Rep*. 2013;3:3457.
28. Burgess N, Maguire EA, O'Keefe J. The human hippocampus and spatial and episodic memory. *Neuron*. 2002;35(4):625-641.
29. Snyder JS, Soumier A, Brewer M, Pickel J, Cameron HA. Adult hippocampal neurogenesis buffers stress responses and depressive behaviour. *Nature*. 2011;476(7361):458-461.
30. Mufson EJ, Mahady L, Waters D, et al. Hippocampal plasticity during the progression of Alzheimer's disease. *Neuroscience*. 2015;309:51-67.
31. Malykhin NV, Coupland NJ. Hippocampal neuroplasticity in major depressive disorder. *Neuroscience*. 2015;309:200-213.

32. Tamminga CA, Zukin RS. Schizophrenia: evidence implicating hippocampal GluN2B protein and REST epigenetics in psychosis pathophysiology. *Neuroscience*. 2015;309:233-242.
33. Kringelbach ML. The human orbitofrontal cortex: linking reward to hedonic experience. *Nat Rev Neurosci*. 2005;6(9):691-702.
34. Stimpson NJ, Davison G, Javadi AH. Joggin' the noggin: towards a physiological understanding of exercise-induced cognitive benefits. *Neurosci Biobehav Rev*. 2018;88:177-186.
35. Huang T, Larsen KT, Ried-Larsen M, Møller NC, Andersen LB. The effects of physical activity and exercise on brain-derived neurotrophic factor in healthy humans: a review. *Scand J Med Sci Sport*. 2014;24(1):1-10.
36. Pietrelli A, Matković L, Vacotto M, Lopez-Costa JJ, Basso N, Brusco A. Aerobic exercise upregulates the BDNF-serotonin systems and improves the cognitive function in rats. *Neurobiol Learn Mem*. 2018;155:528-542.
37. Kanwisher N, Yovel G. The fusiform face area: a cortical region specialized for the perception of faces. *Philos Trans R Soc B Biol Sci*. 2006;361(1476):2109-2128.
38. Kumfor F, Hutchings R, Irish M, et al. Do I know you? examining face and object memory in frontotemporal dementia. *Neuropsychologia*. 2015;71:101-111.
39. Grabe HJ, Wittfeld K, Hegenscheid K, et al. Alexithymia and brain gray matter volumes in a general population sample. *Hum Brain Mapp*. 2014;35(12):5932-5945.
40. De Borba AT, Jost RT, Gass R, et al. The influence of active and passive smoking on the cardiorespiratory fitness of adults. *Multidiscip Respir Med*. 2014;9(1):1-8.
41. Peter I, Papandonatos GD, Belalcazar LM, et al. Genetic modifiers of cardiorespiratory fitness response to lifestyle intervention. *Med Sci Sports Exerc*. 2014;46(2):302-311.
42. Batouli SAH, Saba V. At least eighty percent of brain grey matter is modifiable by physical activity: a review study. *Behav Brain Res*. 2017;332:204-217.
43. Verstynen TD, Lynch B, Miller DL, et al. Caudate nucleus volume mediates the link between cardiorespiratory fitness and cognitive flexibility in older adults. *J Aging Res*. 2012;2012:939285.
44. Whiteman AS, Young DE, Budson AE, Stern CE, Schon K. Entorhinal volume, aerobic fitness, and recognition memory in healthy young adults: a voxel-based morphometry study. *Neuroimage*. 2016;126:229-238.
45. Brockett AT, LaMarca EA, Gould E. Physical exercise enhances cognitive flexibility as well as astrocytic and synaptic markers in the medial prefrontal cortex. *PLoS One*. 2015;10(5):1-11.
46. Wasserman K, Hansen JE, Sue DY, Stringer WW, Sietsema KE, Sun X-G. *Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2011.
47. Delezie J, Handschin C. Endocrine crosstalk between skeletal muscle and the brain. *Front Neurol*. 2018;9:698.
48. Manto M-U, Bower JM, Gerwig M. Consensus paper: roles of the cerebellum in motor control: the diversity of ideas on cerebellar involvement in movement. 2015;11(2):457-487.
49. Voelcker-Rehage C, Niemann C. Structural and functional brain changes related to different types of physical activity across the life span. *Neurosci Biobehav Rev*. 2013;37(9):2268-2295.
50. Ekelund U, Franks PW, Wareham NJ, Åman J. Oxygen uptakes adjusted for body composition in normal-weight and obese adolescents. *Obes Res*. 2004;12(3):513-520.
51. Toth MJ, Goran MI, Ades PA, Howard DB, Poehlman ET. Examination of data normalization procedures for expressing peak VO2 data. *J Appl Physiol*. 1993;75(5):2288-2292.